



# Baseline hypovitaminosis D is not associated with poor clinical outcomes in osteoarticular infections<sup>☆</sup>



J. Marschall<sup>a,b,\*</sup>, J.W.S. Lewis<sup>a</sup>, D.K. Warren<sup>a</sup>, H.M. Babcock<sup>a</sup>, R.L. Barrack<sup>c</sup>, V.J. Fraser<sup>a</sup>

<sup>a</sup> Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, 660 S. Euclid, St. Louis, MO 63110, USA

<sup>b</sup> Department of Infectious Diseases, Bern University Hospital and University of Bern, Bern, Switzerland

<sup>c</sup> Department of Orthopedic Surgery, Washington University School of Medicine, St. Louis, Missouri, USA

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## SUMMARY

**Objectives:** Although vitamin D is recognized as an important factor in bone health, its role in osteoarticular infections is unclear. We hypothesized that low vitamin D (25-hydroxycholecalciferol) levels are associated with a lower likelihood of treatment success in osteoarticular infections.

**Methods:** This was a retrospective cohort study of patients with orthopedic infections who had a 25-hydroxycholecalciferol level drawn when their infection was diagnosed. Outcomes were determined at early (3–6 months) and late ( $\geq 6$  months) follow-up after completing intravenous antibiotics.

**Results:** We included 223 patients seen during an 11-month period with osteoarticular infections and baseline 25-hydroxycholecalciferol levels. During the initial inpatient management of the infection, hypovitaminosis D was identified and treated. The mean 25-hydroxycholecalciferol level was  $23 \pm 14$  ng/ml; 167 (75%) patients had levels  $< 30$  ng/ml. Overall, infection treatment success was 91% (159/174) at early follow-up and 88% (145/164) at late follow-up. 25-Hydroxycholecalciferol baseline levels were similar in those with and without successful clinical outcomes, both at early ( $25 \pm 15$  vs.  $21 \pm 9$  ng/ml;  $p = 0.3$ ) and late follow-up ( $25 \pm 15$  vs.  $23 \pm 16$  ng/ml;  $p = 0.6$ ).

**Conclusions:** To our knowledge this is the first report on hypovitaminosis D and its impact on outcomes of osteoarticular infections. Hypovitaminosis D was frequent in this cohort. With vitamin D repletion, there was no difference in treatment success whether patients had baseline hypovitaminosis or not.

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## 1. Introduction

Osteoarticular infections are a heterogeneous group of infections that can pose considerable management challenges.<sup>1,2</sup> Despite aggressive surgery and antimicrobial use, treatment may fail in up to 20% of cases.<sup>3,4</sup> For prosthetic joint infections, several studies have identified a longer duration of symptoms, sinus tract formation, *Staphylococcus aureus* infection, and a surgical approach inconsistent with expert recommendations as risk factors for treatment failure.<sup>5–7</sup> In osteomyelitis, *Pseudomonas* infections, vancomycin treatment for staphylococcal infections (as opposed to beta-lactams), peripheral vascular disease, and

diabetes mellitus are associated with treatment failure.<sup>8,9</sup> Additional factors such as the host's immune competency may also be relevant; however, few published data address this hypothesis. Specific blood tests that gauge nutritional status have also been shown to predict outcomes of orthopedic surgeries.<sup>10</sup>

Vitamin D, long known for its role in bone health, has more recently been found to also have a role in innate immunity.<sup>11</sup> The underlying mechanisms of its anti-infective activity include triggering the antimicrobial peptide cathelicidin, increasing cytokines, stimulating macrophage proliferation, and up-regulating the vitamin D receptor expressed on macrophages.<sup>12</sup> Studies have sought to determine whether vitamin D deficiency predisposes to infection,<sup>13</sup> and whether vitamin D supplementation can impact clinical outcomes.<sup>14</sup> Most of these studies have been carried out in tuberculosis, influenza, and respiratory infections and the data are conflicting.<sup>15</sup> Interestingly, despite the role of vitamin D in bone metabolism and its presumptive role in the remodeling process following bone disease, no studies have examined the impact of hypovitaminosis D in patients with

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\* Corresponding author at: Corresponding author. Tel.: +41 31 632 9992; fax: +41 31 632 3176.

E-mail address: [jonas.marschall@insel.ch](mailto:jonas.marschall@insel.ch) (J. Marschall).

osteomyelitis. It is unclear if hypovitaminosis D is prevalent in patients with osteoarticular infections and if lower vitamin D levels may be associated with an increased risk of treatment failure.

In this study we sought to retrospectively compare treatment outcomes of patients with hypovitaminosis D at the start of treatment for their osteoarticular infections with those who were vitamin D-sufficient at baseline. Our hypothesis was that cure rates for patients with bone and joint infections who had normal vitamin D levels at baseline would be higher than those of patients with low levels.

## 2. Subjects and methods

### 2.1. Study design

We conducted a retrospective cohort study of adult patients with orthopedic infections who were admitted to Barnes-Jewish Hospital (BJH), a 1250-bed university-affiliated teaching hospital in St. Louis, Missouri. All patients in the cohort were diagnosed with osteomyelitis and/or septic arthritis (including prosthetic joint infections) and had been seen by the Bone and Joint Infectious Disease Consultation Service of the Division of Infectious Diseases, Washington University School of Medicine, between October 1, 2009 and August 31, 2010. This service was established in 2009 to provide dedicated consultation to the orthopedic services in the hospital; although not all-inclusive, this service currently sees the vast majority of orthopedic infections treated at BJH.

Patients were included in the study if there was clinical evidence of an osteoarticular infection based on a combination of criteria (intraoperative findings, pathology, and culture results),<sup>16</sup> and if they had a documented baseline vitamin D (25-hydroxycholecalciferol) level that was drawn in the week before or at initiation of antibiotic therapy. Patients aged <18 years were excluded, as were patients who were seen by our service but had either skin/soft tissue infections without evidence of osteoarticular involvement or were determined to have a non-infectious condition. As part of routine management, all patients with hypovitaminosis D were supplemented with ergocalciferol 2000 IU daily  $\pm$  950 mg elemental calcium twice daily for at least 6–10 weeks.<sup>17</sup> Vitamin D levels were supposed to be repeated after 6–8 weeks in patients receiving supplements, and results were communicated with patients and their primary care physicians. We determined outcomes during a follow-up time of at least 6 months after completion of intravenous antibiotic treatment for all patients. The lack of pre-existing data in the literature on the prevalence of hypovitaminosis D in this population prevented us from conducting sample size calculations.

The study was approved by the Washington University Human Research Protection Office with a waiver of informed consent due to low risk to the enrolled individuals.

### 2.2. Data collection

The research subjects' medical records were screened (by JL and two data abstractors) using a standardized data collection tool. Information regarding demographics, medical history, comorbidities, clinical presentation, laboratory data, radiology findings, surgical and medical management, and treatment outcomes was collected for each subject from inpatient electronic records. Follow-up tests of inflammatory markers (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)) and follow-up imaging studies (if obtained) were gathered from the outpatient information system, as were the clinical response and adverse events (*Clostridium difficile* infection, central venous catheter infection, acute renal failure, elevated liver function tests, cytopenias, skin

rashes, or other allergic reactions). We also evaluated potential risk factors for treatment failure.

### 2.3. Endpoints and definition

The data from the subjects included in the study were entered into a relational database from the standardized data collection tool and then examined for the composite endpoint of 'successful treatment outcome' at early (3–6 months) and late ( $\geq 6$  months) follow-up after completion of antibiotic therapy. Successful treatment was defined as the patient meeting all of the following criteria: complete resolution of signs and symptoms of infection (i.e., complete wound healing without drainage, redness, or persistent pain), improvement in function, normalization of the inflammatory markers ESR and CRP (when available), no repeat surgery for osteomyelitis after discharge, no extension of intravenous antibiotic treatment for >8 weeks, no readmission for osteomyelitis within 6 months, and survival beyond 6 months. 25-Hydroxycholecalciferol levels were defined as follows: sufficient at  $\geq 30$  ng/ml, insufficient at <30 ng/ml and  $\geq 20$  ng/ml, and deficient at <20 ng/ml.<sup>18</sup>

### 2.4. Statistical analysis

Categorical variables were evaluated with the Chi-square test or Fisher's test, as appropriate, and continuous variables with the Student's *t*-test or Mann–Whitney *U*-test, as appropriate. A *p*-value of <0.05 was considered to be statistically significant. The main objective was to determine the impact of baseline 25-hydroxycholecalciferol levels on the primary outcome; however, the data were also evaluated based on other variables associated with successful treatment, including hematogenous vs. contiguous route of infection, presence of *S. aureus* infection, and presence of diabetes as a comorbidity. Due to the small number of clinical failures, we did not perform a multivariate analysis. The statistical package IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) was used for the data analysis.

## 3. Results

A total of 363 patients were screened for inclusion in the study and 223 (61.4%) were recruited based on the inclusion and exclusion criteria. The mean  $\pm$  standard deviation (SD) age was  $57 \pm 16$  years. Patients were predominantly male ( $n = 124$ ; 56%) and white ( $n = 168$ ; 75%) and had a median body mass index of 29 kg/m<sup>2</sup> (range 16–60 kg/m<sup>2</sup>). The most common comorbidities were diabetes mellitus ( $n = 75$ ; 34%), osteoarthritis ( $n = 62$ ; 28%), peripheral vascular disease ( $n = 27$ ; 12%), and chronic renal insufficiency ( $n = 21$ ; 9%); only a few patients had a malignancy ( $n = 6$ ; 3%). Thirteen (6%) carried a diagnosis of rheumatoid arthritis, and nine (4%) were on immunosuppressive therapy. None of the patients were known to be HIV-infected. There were 141 (63%) cases of osteomyelitis, 55 (25%) patients with septic arthritis, and 27 (12%) had dual diagnoses of osteomyelitis and septic arthritis. One hundred and forty-one (63%) patients had hardware-associated infections. The largest subgroups of the cohort were foot infections ( $n = 33$ ; 15%), hip prosthetic joint infections ( $n = 25$ ; 11%), knee prosthetic joint infections ( $n = 25$ ; 11%), hardware-associated tibia/fibula osteomyelitis ( $n = 18$ ; 8%), and hardware-associated vertebral osteomyelitis ( $n = 14$ ; 6%). Most infections were caused by *S. aureus* ( $n = 92$ ; 41%) or coagulase-negative staphylococci ( $n = 35$ ; 16%) (including infections where these pathogens were part of cultures that grew more than one organism). There were 49/223 (22%) polymicrobial infections. Among 168/223 culture-positive infections, there were 119 (71%) monomicrobial infections; 64/119 (54%) of these were due to *S. aureus*, 17/119 (14%) to coagulase-negative staphylococci, 7/119 (6%) to

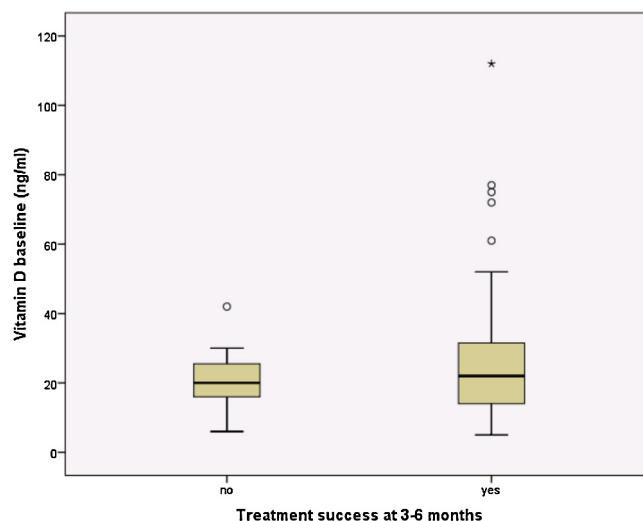
*Pseudomonas aeruginosa*, 7/119 (6%) to streptococci, and 5/119 (4%) to enterococci. Fifty-five (25%) patients had culture-negative infections.

As part of the routine inpatient management, vitamin D levels were obtained. Hypovitaminosis D was identified and treated. The mean baseline 25-hydroxycholecalciferol level was  $23 \pm 14$  ng/ml. One hundred and sixty-seven (75%) patients had levels  $<30$  ng/ml (either insufficient or deficient); 97 (44%) had levels  $<20$  (deficient sensu stricto) (Figure 1).

Hypovitaminosis D was slightly more frequent in patients admitted during fall/winter vs. those seen in spring/summer (98/123 (80%) vs. 69/100 (69%);  $p = 0.07$ ). Age, gender, and race were not associated with vitamin D levels below 30 ng/ml (data not shown). Overall, treatment success in evaluable patients was 91% (159/174) at early follow-up and 88% (145/164) at late follow-up; if loss to follow-up was considered a treatment failure, then 71% (159/223) at early follow-up and 65% (145/223) at late follow-up had treatment success. One hundred and fourteen patients out of 127 (90%) with vitamin D levels  $<30$  ng/ml vs. 45/47 (96%) with levels  $\geq 30$  ng/ml had successful outcomes at 3 months ( $p = 0.4$ ), and 103/117 (88%) vs. 42/47 (89%), respectively, had successful outcomes at 6 months ( $p = 0.8$ ). Limiting the comparison to vitamin D deficiency sensu stricto, 64/70 (91%) with vitamin D levels  $<20$  ng/ml vs. 95/104 (91%) with levels  $\geq 20$  ng/ml had successful outcomes at 3 months ( $p = 1.0$ ), and 55/64 (86%) vs. 90/100 (90%), respectively, had successful outcomes at 6 months ( $p = 0.4$ ). Vitamin D baseline levels were similar in those with or without successful clinical outcomes, both at early ( $25 \pm 15$  vs.  $21 \pm 9$  ng/ml;  $p = 0.3$ ) (Figure 2) and late follow-up ( $25 \pm 15$  vs.  $23 \pm 16$  ng/ml;  $p = 0.6$ ) (Figure 3).

Follow-up levels were obtained for only 50 (22%) patients (after at least 6–8 weeks), with a mean level of  $32 \pm 14$  ng/ml; many (21/50; 42%) were still deficient at that point. Follow-up vitamin D levels of these 50 patients were not different between those with treatment success and those with treatment failure, at either the 3–6 months clinical follow-up ( $32 \pm 16$  vs.  $30 \pm 7$  ng/ml;  $p = 0.8$ ) or at the  $\geq 6$  months clinical follow-up ( $33 \pm 11$  vs.  $28 \pm 8$  ng/ml;  $p = 0.4$ ). If loss to follow-up was considered a treatment failure, success rates at the early follow-up point were similar in patients with replete vs. deficient/insufficient follow-up vitamin D levels (22/29 (76%) vs. 17/21 (81%);  $p = 0.7$ ). However, at late follow-up there were fewer successes in deficient/insufficient patients (12/21 (57%) vs. 25/29 (86%);  $p = 0.02$ ).

We compared risk factors for clinical failure at early and late follow-up time points. At early follow-up, a hematogenous etiology of the infection was associated with failure (3/15 (20%) failures vs. 5/159 (3%) successes;  $p = 0.02$ ). *S. aureus* infections (including polymicrobial staphylococcal infections) did not impact outcomes at early follow-up (9/75 (12%) failures with *S. aureus* vs.



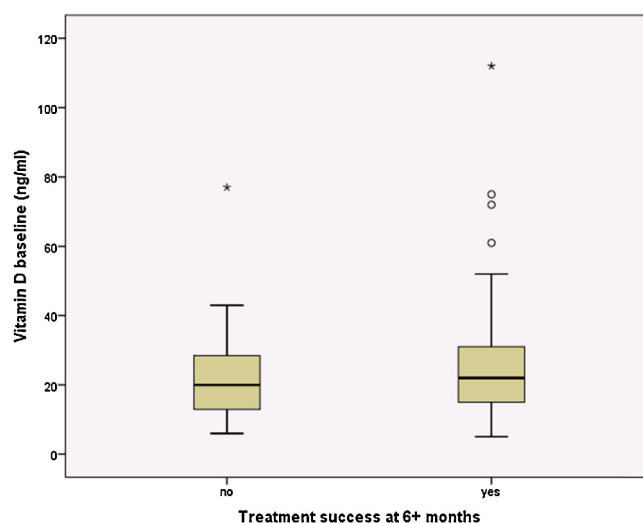
**Figure 2.** Mean baseline vitamin D serum levels (ng/ml) by subsequent clinical outcomes at early (3–6 months) follow-up, in 174 patients with osteoarticular infections.  $p$ -Value = 0.3. °Outliers. \*Extreme cases.

6/99 (6%) failures with other pathogens;  $p = 0.2$ ). At late follow-up, however, a hematogenous etiology was no longer associated with failure (3/19 (16%) failures vs. 7/145 (5%) successes;  $p = 0.09$ ), but *S. aureus* infection was more likely to be associated with clinical failure (13/67 (19%) failures with *S. aureus* vs. 6/97 (6%) with other pathogens;  $p < 0.01$ ). Age, gender, race, and comorbidities such as diabetes mellitus (Table 1), renal insufficiency, and peripheral vascular disease (data not shown) were not associated with clinical failure.

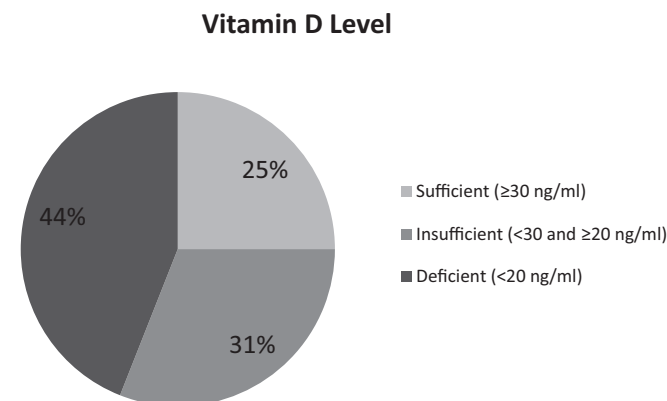
All patients underwent some form of surgical debridement. For 23 (10%) patients, hardware was retained after debridement. Total hardware explantation was done in 80 (36%) patients and hardware was partially explanted in another 33 (15%) patients.

#### 4. Discussion

Several studies have attempted to elicit risk factors for treatment failure in bone and joint infections,<sup>5–9</sup> but have not focused on the immune system or vitamin D levels. Vitamin D is



**Figure 3.** Mean baseline vitamin D serum levels (ng/ml) by subsequent clinical outcomes at late ( $\geq 6$  months) follow-up, in 164 patients with osteoarticular infections.  $p$ -Value = 0.6. °Outliers. \*Extreme cases.



**Figure 1.** Distribution of baseline vitamin D levels in 223 patients with osteoarticular infections.

**Table 1**Univariate analysis of risk factors for treatment failure at early (3–6 months) follow-up in patients with osteoarticular infections (n = 174)<sup>a</sup>

	Success (n = 159)	Failure (n = 15)	p-Value
Age, years	57.0 ± 15.7	57.5 ± 16.3	0.9
Gender, male	84 (53%)	11 (73%)	0.1
Race, white	125 (79%)	9 (60%)	0.1
Diabetes mellitus	107 (67%)	8 (53%)	0.3
Rheumatoid arthritis	12 (8%)	0	0.6
Baseline vitamin D level, ng/ml	25 ± 15	21 ± 9	0.3
Hematogenous etiology of the osteoarticular infection	5 (3%)	3 (20%)	0.02
<i>Staphylococcus aureus</i> infection	66 (42%)	9 (60%)	0.2

SD, standard deviation.

<sup>a</sup> Results are presented as the mean ± SD, or as the number (%).

relevant for bone health and has recently been recognized to have multiple roles in the innate and adaptive immune response to infection. To date, treatment outcomes of orthopedic infections have not been analyzed with regard to patient vitamin D serum levels. We hypothesized that hypovitaminosis D may negatively impact treatment outcomes. In this study, we did not find an association between low vitamin D serum levels at the start of infection treatment and outcomes of orthopedic infections, when vitamin D supplementation was provided along with antimicrobial therapy.

Vitamin D is not only important for bone remodeling but also has immunomodulatory properties that have been elucidated recently.<sup>19</sup> There are different functional aspects that result in its anti-infective activity.<sup>12</sup> Mobilizing neutrophil granulocytes and upregulating the antimicrobial peptide cathelicidin may be the most prominent pathways by which this occurs. However, a systematic review published in 2009 concluded that vitamin D supplementation for the prevention or treatment of infectious diseases cannot be recommended due to a lack of evidence.<sup>15</sup> More recently, a number of publications have examined the value of vitamin D supplementation in patients with HIV infection,<sup>20</sup> pneumonia,<sup>21</sup> and tuberculosis,<sup>22,23</sup> without coming to clear conclusions on its value in improving clinical outcomes in these infections.

In our study, there was no detrimental effect of baseline hypovitaminosis D on bone and joint infection outcomes, although all of these patients were prescribed vitamin D repletion therapy concomitantly with their antimicrobial therapy. Hypovitaminosis D may still be a potentially modifiable risk factor for poor clinical outcomes of osteoarticular infections if left untreated. There is no published literature that describes the systematic detection of vitamin D levels in patients with bone and joint infections and we therefore cannot place our findings in a larger context. There have been, however, case reports that have noted osteoarticular infections in tuberculosis patients with very low vitamin D serum levels.<sup>24</sup> It should also be pointed out that there were more late failures in the small group of patients who were still deficient at follow-up testing; this finding suggests that there may be an impact of ongoing (or untreated) hypovitaminosis D on bone and joint infection outcomes. This study also demonstrated that low vitamin D levels were quite prevalent in this patient population. We surmise that hypovitaminosis D is a treatable condition with a possible impact on outcomes in patients with orthopedic infections.

Even though there is insufficient evidence to support screening for vitamin D deficiency in all types of infections, patients at risk for orthopedic infections have many traditional risk factors for low vitamin D levels. Vitamin D-deficient patients with orthopedic infections may benefit from improved bone remodeling and bone structure and/or immune support if their low vitamin D levels are

corrected with replacement therapy. The 2011 guidelines for evaluating, treating, and preventing hypovitaminosis D by the US Endocrine Society, however, do not specifically address patients with bone and joint infections.<sup>25</sup> The notion that hypovitaminosis D may affect large proportions of hospitalized patients is, nevertheless, not new, and has been documented both for medical<sup>26</sup> and surgical patients.<sup>27</sup>

The small number of treatment failures that were observed in our study (9% at early and 12% at late follow-up) prevented us from conducting a multivariate analysis of risk factors for clinical failure. Similar to previous studies, *S. aureus* infection was associated with clinical treatment failures.<sup>5</sup> Previous studies have shown that outcomes not only depend on the virulence of specific pathogens, but also that they can be correlated with the duration of symptoms before treatment is initiated, whether there is sinus tract formation, and the type of surgical approach chosen. We did not collect this information because it was not the main objective of our study. Recently, another group reported that prosthetic joint infections are more likely to result in poor outcomes if the affected patients are potentially immunocompromised (which included rheumatoid arthritis, diabetes mellitus, renal insufficiency, and malignancy).<sup>28</sup> There was no association between diagnosis of rheumatoid arthritis or diabetes mellitus and clinical failure in our study. Why the hematogenous development of an infection was more likely to result in failure at the early follow-up time is unclear. A potential explanation could be that the focus of infection persisted and therefore gave rise to infection recurrence.

Limitations of our study include the retrospective cohort design and the fact that no multivariate analysis of outcomes could be performed due to the small number of treatment failures. Patients were not included if vitamin D testing was missed; this could have introduced a selection bias. There are no standard diagnostic criteria for orthopedic infections, which could have led us to include patients with 'culture-negative', non-infectious orthopedic problems.<sup>29</sup> The retrospective nature of the study also prevented us from tracking adherence to vitamin D supplementation. Lastly, because vitamin D supplementation was given to all deficient/insufficient patients, we cannot discern what effect untreated hypovitaminosis D would have had on outcomes.

In conclusion, we believe this to be the first report on hypovitaminosis D and its impact on outcomes of osteoarticular infections. Hypovitaminosis D was frequent in this patient cohort. There was no difference in treatment success at early or late follow-up depending on baseline vitamin D levels as long as vitamin D supplementation was given to those with vitamin D deficiency. It is currently unresolved whether vitamin D has a specific role in the management of bone and joint infections; this could be tested in a randomized trial. Clinicians should continue to monitor high risk patients for hypovitaminosis D as supplementation has beneficial effects on bone health.

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**Conflict of interest:** The authors declare that they have no conflict of interest.

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